

REMARKS**Amendments to the Specification**

The paragraph on page 15, lines 11-29 have been amended to correct a clear typographical error in the spelling of adalimumab and to update the trademark status of HUMIRA®.

No new matter has been added. Entry of the Amendments is respectfully requested.

Amendments to the Claims

Claims 1, 46, 50, 91 and 92 have been amended. New Claims 93-96 have been added. Claims 49, 80-83 and 89-90 have been canceled. Claim 50 has been amended so that it will not depend from a canceled claim.

Support for the amendment to Claim 1 is found in the specification, for example, at page 15, lines 14-19 and page 16, lines 1-9.

Claim 46 has been amended to indicate that the sustained release device maintains the administered inhibitor of TNF- α synthesis at a therapeutically effective level. Support for the amendment is found in the specification, for example, at page 22, line 27; page 24, lines 24-25; and page 28, line 16.

Claims 91 and 92 have been amended to recite specific growth factors, namely, BMP-1, BMP-3, BMP-2; OP-1, BMP-2A, BMP-2B, or BMP-7 (Claim 91) and TGF-B (Claim 92). Support for the amendments is found in the specification, for example, at page 32, lines 11-26.

New Claims 93-96 recite specific inhibitors of TNF- α synthesis. Support for new Claims 93-96 is found in the specification, for example, at page 15, line 5 to page 16, line 9.

No new matter has been added. Entry of the Amendments is respectfully requested.

Office Action Summary from Office Action Mailed June 27, 2006

In the Office Action Summary, Disposition of Claims, the Examiner included Claims 14, 44 and 59 as rejected. However, Applicants note that Claims 14, 44 and 59 were canceled in the Amendment filed on April 4, 2006.

Rejection of Claims 38 and 48 under 35 U.S.C. §112, second paragraph

In the Office Action mailed June 27, 2006, the Examiner rejected Claims 38 and 48 under 35 U.S.C. §112, second paragraph, as being indefinite. However, in the subsequent March 10, 2008 Examiner's Answer in response to Applicants' Appeal Brief, the Examiner indicated "[u]pon further consideration, the rejection of claims 38 and 48 under U.S.C. §112, 1st and 2nd paragraph is withdrawn." Therefore, it is believed that this rejection will be moot. However, in an abundance of caution, since the Examiner's Answer has been vacated and is no longer of record, Applicants present the following response.

As amended, Applicants' independent claim, Claim 1, is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or an antigen-binding fragment thereof. Claims 38 and 48 depend upon Claim 1, and, therefore, contain the same limitation. Claim 38 is directed to the method of Claim 1, wherein the inhibitor of TNF- α synthesis is present in the formulation in an amount of at least 100 mg/ml. Claim 48 is directed to the method of Claim 1, wherein the inhibitor of TNF- α synthesis is present in the formulation in a maximum amount of 0.5 mg. The Examiner has rejected these claims as indefinite, stating that "[i]n the absence of a specific recited structure, the recitation of a specific dosage is meaningless."

With regard to the definiteness requirement of 35 U.S.C. § 112, second paragraph, the Examiner's focus during examination of the claims for compliance with the requirement for definiteness is "whether the claim meets the threshold requirements of clarity and precision...." See *Manual of Patent Examining Procedure* (MPEP) §2173.02.

When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the manner of terms should be permitted even though the claim language is not as precise as the examiner might desire.

Id. (emphasis in original)

Claims 38 and 48 recite administration of particular amounts of “an inhibitor of TNF- α synthesis.” Since none of the other claims reciting “an inhibitor of TNF- α synthesis” are rejected as indefinite, it appears that the rejection is directed to the use of amounts. Definiteness of claim language must be analyzed not in a vacuum, but in light of the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *Id.* One of ordinary skill in the art should understand what is meant by amounts of such antibodies in units such as “mg/ml” and “mg”. Thus, it would be very straightforward for one of ordinary skill in the art to understand what is meant by an inhibitor of TNF- α synthesis “present in the formulation in an amount of at least 100 mg/ml” and “present in the formulation in a maximum amount of 0.5 mg” (see, for example, the specification at page 23 lines 15-21 and page 29, lines 5-11). Thus, each claim “apprises one of ordinary skill in the art of its scope and, therefore, serves its notice function...” and “defines the patentable subject matter with reasonable degree of particularity and distinctness.” *Id.* Further, as amended, the claims are directed to specific recited structures, antibodies.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 38 and 48 under 35 U.S.C. § 112, first paragraph

In the Office Action mailed June 27, 2006, the Examiner rejected Claims 38 and 48 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. However, as indicated above, in the subsequent March 10, 2008 Examiner’s Answer in response to Applicants’ Appeal Brief, the Examiner indicated “[u]pon further consideration, the rejection of claims 38 and 48 under U.S.C. §112, 1st and 2nd paragraph is withdrawn.” Therefore, it is believed that this rejection will be moot. However, in an abundance of caution, since the Examiner’s Answer has been vacated and is no longer of record, Applicants present the following response.

As indicated above, as amended, Applicants’ independent claim, Claim 1, is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or antigen-binding fragment thereof. Claims 38 and 48 depend upon Claim 1, and, therefore, contain the same limitation. As indicated above, Claims 38 and 48 recite

administration of particular amounts of an inhibitor of TNF- α synthesis. The claims do not require the artisan to make the compounds; they merely require the artisan to measure them. Otherwise, these claims do not differ from Claim 1, which is not rejected for enablement. The level of skill in the art is high. Anti-TNF- α monoclonal antibodies are well-known and available in the art, as are procedures to measure them. In addition, one of skill in the art could easily determine how to measure an anti-TNF- α monoclonal antibody, in a formulation in an amount of at least 100 mg/ml or in a formulation in a maximum amount of 0.5 mg without undue experimentation. (See, for example, the specification at page 23, lines 15-21 and page 29, lines 5-11). The claims are enabled.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 46 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claim 46 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

As amended, Applicants' independent claim, Claim 1, is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or antigen-binding fragment thereof. Claim 46 depends upon Claim 1, and, therefore, contains the same limitation. As amended, Claim 46 recites "The method of claim 39, wherein the sustained release device maintains the administered inhibitor of TNF- α synthesis at a therapeutically effective level." Such a device was known in the art. For example, Pike teaches such a sustained release device. Particularly as amended, Claim 46 is enabled.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 49, 91 and 92 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 49, 91 and 92 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

As amended, Applicants' independent claim, Claim 1, is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or antigen-binding fragment thereof. Claims 49, 91 and 92 depend upon Claim 1, and, therefore,

contain the same limitation. As discussed above, Applicants have canceled Claim 49 and amended Claims 91 and 92 to recite a specific, well-known GDF and specific, well-known BMPs.

The Examiner states that Claims 49, 91 and 92 are not enabled because the specification fails to teach the skilled artisan how to use the factors recited without undue experimentation to determine whether a given protein would be useful in the claimed methods and what the dosage would be. Applicants respectfully disagree. The specification discusses the factors in detail (*e.g.*, page 32, line 11-page 33, line 2). The level of skill in the relevant art is high, and therapeutic administration of growth factors was well-known at the time of the invention (See, for example, Dunn *et al.* and Pike *et al.* (*e.g.*, paragraphs 43-59 above)). A person having ordinary skill in the art could easily determine whether an inflamed knee joint is being treated and a person having ordinary skill in the art could determine appropriate dosage of these known factors for such treatment, with only routine experimentation. The claims are enabled.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 49, 91 and 92 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 49, 91 and 92 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants note that the Examiner on page 9 of the Office Action rejected Claims 49, 90 and 91 and then in the same paragraph discussed claims 49, 91 and 92. Based on the Examiner's discussion of the rejection, Applicants believe that the Examiner intended to reject Claims 49, 91 and 92.

Applicants also note that on page 10 of the Office Action, the Examiner rejected Claim 90 based on new matter. While Applicants respectfully disagree, Claim 90 has been canceled in order to further prosecution.

As discussed above, Applicants have canceled Claim 49 and amended Claims 91 and 92 to recite a specific, well-known GDF and specific, well-known BMPs.

As noted above, at the time of the invention, therapeutic administration of growth factors was well known. As noted by the Examiner, the specification lists a myriad of growth factors that may be used in the invention (*see, e.g.*, page 32, line 11-page 33, line 2). As further noted by the Examiner, the skilled artisan would be aware of a number of different compounds which would be classified under the heading "growth factors". Applicants are not required to put into a

specification what is well known. Clearly, the claimed subject matter is described in the specification in a manner which does demonstrate that the Applicants had possession of the specific subject matter claimed, and the requirement for written description has been met. Applicants note that “bone morphogenetic protein” is well known and well characterized in the art. *See* Jiang, C. H., “Osteogenic Activity of the Fourteen Types of Human Bone Morphogenetic Proteins (BMPs),” *J. Bone Joint Surg Am.*, 85: 1544-52 (2003) (Abstract) (Exhibit A). In the Examiner’s Answer, non-vacated, the Examiner withdrew this rejection in view of Applicants’ arguments, which are substantially similar to those herein.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 under 35 U.S.C. §103(a)

The Examiner has rejected Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 under 35 U.S.C. §103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics*, 140:125-127 (2002) in view of Dunn (EP 1 153 606). The Examiner states that “[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide taught by Lehman *et al.* using the administration route taught by Dunn”.

Applicants respectfully disagree. First, “[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious.” Manual of Patent Examining Procedure (MPEP) §2143.03 (Eighth edition, Revision July 2008) (citations omitted). Second, as discussed in detail below, the *Graham* analysis reveals that none of the references teach or suggest Applicants’ claimed invention, particularly as amended, and, thus, the Examiner has not established a *prima facie* case of obviousness.

The Graham Analysis Reveals That None of the References Teach or Suggest Applicants’ Claimed Invention

In *KSR v. Teleflex*, 127 S.Ct. 1727 (2007), the court clarified the appropriate analysis for determining obviousness under 35 U.S.C. § 103. The court restated that the *Graham* framework controls the analysis. Explicit findings as to (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) secondary considerations, such as commercial success, long felt but unsolved needs,

failure of others, etc., should be made in the *Graham* analysis. The legal question of obviousness is then assessed against this factual background.

The Court did not overturn the “TSM” (teaching-suggestion-motivation) test for determining whether an invention is obvious under 35 U.S.C. § 103; rather, the Court disapproved of the narrow manner in which it was applied by the Federal Circuit in *KSR*. *KSR*, 127 S.Ct. at 1741. The Court indicated that the TSM test provided “helpful insight” and further said that there is no inconsistency between the TSM test and the *Graham* analysis. *Id.* The Court did not discount that the test might serve as a useful analytical device in the context of a proper obviousness analysis. *Id.*

Scope and Content of The Prior Art

Lehman

Lehman et al. teaches that two children with systemic onset juvenile rheumatoid arthritis were systemically treated with etanercept (ENBREL®) and thalidomide. Although the treatment with etanercept was unsuccessful, the treatment with thalidomide demonstrated improvements. Applicants note that etanercept as well as monoclonal antibodies are biologics. Thalidomide is not an antibody or even a biologic – it is a small molecule.

Dunn

Dunn teaches treating an inflamed joint by injecting growth hormone and buffer solution into the joint space. (See Dunn, column 3, paragraph 0009 and 0011). According to Dunn, the hormone is injected into the joint space so that it may be absorbed into the bloodstream resulting in systemic effects, such as stimulation of production of bone marrow outside the joint. (See Dunn, column 7, paragraph 0027). Dunn further discloses that, as a “preliminary” step, agents such as anti-kinases, growth factors and anti-cytokines including ENBREL® can be injected or otherwise applied to the joint prior to, or simultaneously with, the step of injecting a growth hormone and buffer solution into the joint space. (See Dunn abstract; column 8, paragraph 0030; and column 9, paragraph 0031).

The Differences Between The Prior Art And The Claims at Issue

Applicants' independent claim, Claim 1, is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or antigen-binding fragment thereof. Claims 2, 34, 37, 47, 49, 51, 54 and 56 depend upon Claim 1, and, therefore, contain the same limitation.

As discussed above, Lehman *et al.* teaches that systemic treatment with etanercept (ENBREL[®]) was unsuccessful, but systemic treatment with thalidomide demonstrated improvements. Thalidomide is a small molecule, not a biologic like ENBREL[®] or an anti-TNF- α monoclonal antibody. Thus, both the means of administration (systemic) and the agent successfully administered (thalidomide) differ from those of the claimed invention. In fact, given that ENBREL[®] was not an effective treatment, Lehman teaches away from using an anti-TNF- α biologic to treat such inflammatory disorders.

Similarly, the secondary cited reference, Dunn, also does not disclose an anti-TNF- α monoclonal antibody. In fact, it does not disclose a biologic which inhibits TNF- α synthesis. ENBREL[®] (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor (TNFR) linked to the Fc portion of human IgG1. ENBREL[®] is not known to inhibit TNF- α synthesis and ENBREL[®] is not an anti-TNF- α monoclonal antibody. While page 13 of the Office Action mailed June 27, 2006 states that "[t]he reference teaches the injection of a group of agents such as anti-cytokines (column 3, 2008, lines 45-57), which would by definition include an inhibitor of TNF- α synthesis" (emphasis omitted), nowhere does Dunn mention injecting an anti-TNF- α monoclonal antibody. Further, there were a myriad of anti-cytokines known in the art at the time of the invention. See, for example, Van Lent, PL. *et al.*, "Major Role for Interleukin 1 But Not For Tumor Necrosis Factor in Early Cartilage Damage in Immune Complex Arthritis in Mice," *J. Rheumatol.*, 22: 2250-8 (Abstract) (Exhibit B), which discloses that potential candidate of anti-cytokines at the time include, for example, anti-IL-1 antibodies. Of all the anti-cytokines known in the art at the time of the invention, it would not have been obvious based on the teachings of Dunn to select an anti-TNF- α monoclonal antibody.

Further, in order to conclude that a claim would have been obvious in view of the prior art, a reasonable expectation of success is required (see The Manual of Patent Examining Procedure (M.P.E.P.) §2143.02 (Eighth Edition, July 2008 revision) and *KSR v. Teleflex*, 127 S.Ct. at 1739). One of skill in the art would not have been motivated to substitute ENBREL[®], a dimeric receptor fusion protein that, according to the full prescribing information (Exhibit C), is administered by subcutaneous injection, with an anti-TNF- α monoclonal antibody, such as infliximab, which according to the full prescribing information (Exhibit D), is administered by systemic IV infusion, in the methods of Dunn with a reasonable expectation of success. Further, as discussed in Applicant's specification, at the time of Applicants' invention, one of skill in the art would not have been motivated to administer locally any inhibitor of TNF- α synthesis. For example, as noted in Applicants' specification, at least one published application, US Publication No. 2003/0039651 (Olmarker), teaches in its examples that TNF inhibitors are to be administered through systemic pathways. More specifically, Applicants' specification discloses that US Publication No. 2003/0039651 (Olmarker) teaches that that "the major contribution of TNF-alpha may be derived from recruited, aggregated and maybe even extravasated leukocytes, and that successful pharmacologic block may be achieved only by systemic treatment" (Applicants' specification, page 4, lines 8-17, emphasis added).

As taught in Applicants' specification, direct administration of the inhibitor of TNF- α synthesis trans-capsularly is advantageous over systemic treatment. Such advantages include, for example, arresting the inflammation process begun within the joint and the degeneration of the hyaline cartilage, preventing intracapsular nerve irritation, increasing the half life of the inhibitor of TNF- α synthesis in the capsule and reducing unwanted side effects (see the specification, for example at page 8, line 10 to page 10, line 5). Moreover, anti-TNF- α monoclonal antibodies, such as infliximab, are more specific for TNF- α whereas ENBREL[®] binds both TNF- α and lymphotoxin (TNF- β). (See page 2 of the full prescribing information for ENBREL[®] (Exhibit C) and page 1 of the full prescribing information for infliximab (Exhibit D)). Thus, there is no reasonable expectation of success in substituting an anti-TNF- α monoclonal antibody, such as infliximab, with ENBREL[®] in the methods of Dunn. Thus, the claimed invention is not obvious. Hindsight reconstruction, having Applicant's invention in mind, is not permissible.

The combined references cited do not teach or suggest a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Moreover, there is no motivation to modify the references in a manner which would do so. A *prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody or any biologic which inhibits TNF- α synthesis in the claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 36, 39-43, 45, 58 and 60-65 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 36, 39-43, 45, 58 and 60-65 under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics*, 140:125-127 (2002) in view of Pike *et al.* (US Publication No. 20030134792). The Examiner states that “[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide, and inhibitor of the production of the cytokine TNF- α , as taught by Lehman, by using the delivery systems disclosed by Pike *et al.*”

Applicants respectfully disagree. Claims 36, 39-43, 45, 58 and 60-65 recite various aspects of administration. They depend upon amended Claim 1, and, therefore, are also directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or antigen-binding fragment thereof.

The teachings of Lehman and Dunn are discussed in detail above. Lehman *et al.* teaches that systemic treatment with etanercept (ENBREL[®]) was unsuccessful, but systemic treatment with thalidomide demonstrated improvements. Thalidomide is a small molecule, not a biologic like ENBREL[®] or an anti-TNF- α monoclonal antibody. Thus, both the means of administration (systemic) and the agent successfully administered (thalidomide) differ from those of the claimed invention. In fact, given that ENBREL[®] was not an effective treatment, Lehman teaches away from using an anti-TNF- α biologic to treat such inflammatory disorders. Nor does it teach the different aspects of formulation and administration disclosed in the rejected claims.

Pike *et al.* discloses the treatment of articular cartilage disorders by administering IGF-1, a growth factor. Such treatment includes administering IGF-1 by, for example, intra-articular injection. Although Pike *et al.* generally teaches that additional therapeutic agents such as “antibiotics, including anti-inflammatory agents, and the like” can be included in its composition, Pike *et al.* does not provide any further description of such agents and does not teach or suggest administering an inhibitor of TNF- α , including an inhibitor of TNF- α synthesis which is an anti-TNF- α monoclonal antibody. (Pike at paragraph 0038). Thus, the combined references do not describe or suggest transcapsular administration of an anti-TNF- α monoclonal antibody which inhibits TNF- α synthesis.

The combined references do not teach or suggest a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Moreover, there is no motivation to modify the references in a manner which would do so. A *prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody or any biologic which inhibits TNF- α synthesis in the claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 50 under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 50 under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics*, 140:125-127 (2002) in view of Dunn (EP 1 153 606), and Molloy *et al.*, *Sports Med.*, 33:381-394 (2003). The Office Action states that “[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify a formulation comprising thalidomide, as taught by Lehman by adding a growth factor such as PDGF as suggested by Dunn and Molloy *et al.*”

Applicants respectfully disagree. As noted above, as amended, Applicants’ invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Claim 50 is directed to the method wherein the formulation further comprises a growth factor provided by platelet concentrate.

As discussed above, Lehman *et al.* teaches that systemic treatment with etanercept (ENBREL[®]) was unsuccessful, but systemic treatment with thalidomide demonstrated improvements. As noted above, thalidomide is a small molecule, not a biologic like ENBREL[®] or an anti-TNF- α monoclonal antibody. Thus, both the means of administration (systemic) and the agent successfully administered (thalidomide) differ from those of the claimed invention. In fact, given that ENBREL[®] was not an effective treatment, Lehman teaches away from using an anti-TNF- α biologic to treat such inflammatory disorders.

Dunn also does not disclose an anti-TNF- α monoclonal antibody. In fact, it does not disclose a biologic which inhibits TNF- α synthesis. ENBREL[®] (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor (TNFR) linked to the Fc portion of human IgG1. ENBREL[®] is not known to inhibit TNF- α synthesis and ENBREL[®] is not an anti-TNF- α monoclonal antibody. While the page 13 of the Office Action mailed June 27, 2006 states that “[t]he reference teaches the injection of a group of agents such as anti-cytokines (column 3, 2008, lines 45-57), which would by definition include an inhibitor of TNF- α synthesis” (emphasis omitted), nowhere does Dunn mention injecting an anti-TNF- α monoclonal antibody. Further, there were a myriad of anti-cytokines known in the art at the time of the invention. See, for example, Van Lent, PL. *et al.*, “Major Role for Interleukin 1 But Not For Tumor Necrosis Factor in Early Cartilage Damage in Immune Complex Arthritis in Mice,” *J. Rheumatol.*, 22: 2250-8 (Abstract) (Exhibit B), which discloses that anti-cytokines include, for example, anti-IL-1 antibodies. Of all the anti-cytokines known in the art at the time of the invention, it would not have been obvious based on the teachings of Dunn to select an anti-TNF- α monoclonal antibody.

Lehman and Dunn do not teach the specific use of a formulation comprising a growth factor provided by platelet concentrate. Moreover, neither Lehman nor Dunn describe or suggest Applicants’ methods of administration of an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody.

Molloy teaches that growth factors play a role in tendon healing. Molloy does not describe or suggest Applicants’ methods of administration of an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Therefore, it

does not supply the necessary teachings lacking in the Lehman and Dunn references to arrive at the claimed invention.

None of the combined cited references teach or suggest a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Moreover, there is no motivation to modify the references in a manner which would do so. A *prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody or any biologic which inhibits TNF- α synthesis in the claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 53 and 57 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 53 and 57 under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics*, 140:125-127 (2002) in view of Smith *et al.* (U.S. Publication No. 20020169162). The Office Action states that “[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to administer a formulation comprising thalidomide as taught by Lehman *et al.* using the pump device disclosed by Smith *et al.*”

Applicants respectfully disagree. As noted above, as amended, Applicants’ invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Claim 53 is directed to the method of Claim 1, wherein the formulation is injected into the synovial fluid. Claim 57 is directed to the method of Claim 1, wherein the formulation is administered through a drug pump.

As discussed above, Lehman *et al.* teaches that systemic treatment with etanercept (ENBREL[®]) was unsuccessful, but systemic treatment with thalidomide demonstrated improvements. Thalidomide is a small molecule, not a biologic like ENBREL[®] or anti-TNF- α monoclonal antibodies. Thus, both the means of administration (systemic) and the agent successfully administered (thalidomide) differ from those of the claimed invention. In fact, given that ENBREL[®] was not an effective treatment, Lehman teaches away from using an anti-

TNF- α biologic to treat such inflammatory disorders. Moreover, it does not mention administration in the synovial fluid-containing portion of the joint, or through a drug pump.

Smith *et al.* teaches a sustained release device which may be surgically implanted intraarticularly, *i.e.*, within the synovial joint. (See Smith *et al.* at paragraph 0046). Smith *et al.* teaches that the compounds that can be administered via the sustained release device include glucocorticoids, anti-inflammatories such as dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof; non-steroidal anti-inflammatory drugs and cyclosporines. (See Smith at paragraph 0043). Thus, Smith only exemplifies small molecules, not any biologics such as antibodies, for such administration. Moreover, Smith *et al.* does not teach or suggest administering an inhibitor of TNF- α synthesis. Thus, neither Lehman *et al.* nor Smith *et al.* describes or suggests Applicants' invention.

The combined references do not teach or suggest a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Moreover, there is no motivation to modify the references in a manner which would do so. *A prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody or any biologic which inhibits TNF- α synthesis in Applicants' claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 55 under 35 U.S.C. § 103(a) as being obvious

The Examiner has rejected Claim 55 under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics*, 140:125-127 (2002) in view of Dunn (EP 1 153 606) and Cardone *et al.*, *American Family Physician*, 67:2147-2152 (2003). The Office Action states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administration of thalidomide as taught by Lehman *et al.* and Dunn by aspirating fluid from the knee joint prior to administration as suggested by Cardone *et al.*."

Applicants respectfully disagree. Claim 55 is directed to the method of Claim 1, wherein a portion of the synovial fluid is removed prior to administration of the inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody or

antigen-binding fragment thereof. The references cited by the Examiner do not teach or suggest the claimed invention.

The teachings of Lehman and Dunn are discussed in detail above. Neither Lehman nor Dunn teach or suggest removing a portion of the synovial fluid prior to trans-capsular administration of an inhibitor of TNF- α synthesis. Moreover, neither Lehman nor Dunn describe or suggest Applicants' methods of administration of an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody.

Cardone *et al.* teaches injection procedures for administering corticosteroids into the hip and knee joints as diagnostic and therapeutic tools. In addition, Cardone *et al.* teaches aspiration procedures for the knee for the purpose of diagnosing an unexplained effusion and to relieve discomfort caused by the effusion. Thus, Cardone *et al.* does not teach or suggest any biologic, and specifically does not teach any antibodies. Cardone *et al.* does not teach or suggest removing a portion of the synovial fluid prior to trans-capsular administration of an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Therefore, Cardone *et al.* does not supply the teachings missing in Lehman and Dunn to arrive at the claimed invention.

The combined cited references do not teach or suggest a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Moreover, there is no motivation to modify the references in a manner which would do so. A *prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody or any biologic which inhibits TNF- α synthesis in Applicants' claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1 and 89 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1 and 89 under 35 U.S.C. § 103(a) as being obvious over Dunn (EP 1 153 606) in view of Braun and Sieper, *Expert Opin. Biol. Ther.* 3(1): 141-168 (2003). According to the Office Action, "[i]t would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an

inflamed orthopedic joint taught by Dunn to administer the monoclonal antibody taught by Braun in place of the soluble TNF receptor taught by Dunn.” The Examiner further states that “[t]he person of ordinary skill in the art would have been motivated to make these modifications because both Enbrel and [Infliximab] act to inhibit the activity of the cytokine TNF- α and reduce inflammation.”

Applicants respectfully disagree. Claim 89 has been canceled and the subject matter of Claim 89 has been incorporated into Claim 1. As noted above, Applicants’ invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering into the joint space a formulation comprising an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody.

The teachings of Lehman and Dunn are discussed in detail above. In order to conclude that a claim would have been obvious in view of the prior art, a reasonable expectation of success is required (see The Manual of Patent Examining Procedure (M.P.E.P.) §2143.02 (Eighth edition, July 2008 revision) and *see KSR v. Teleflex*, 127 S.Ct. at 1739). One of skill in the art would not have been motivated to substitute ENBREL[®], a dimeric receptor fusion protein that, according to the product insert (Exhibit C), is administered by subcutaneous injection, with an anti-TNF- α monoclonal antibody, such as infliximab, which according to the product insert (Exhibit D), is administered by systemic IV infusion, in the methods of Dunn with a reasonable expectation of success. Further, as discussed in Applicant’s specification, at the time of Applicants’ invention, one of skill in the art would not have been motivated to administer locally any inhibitor of TNF- α synthesis.

As taught in Applicants’ specification, direct administration of the inhibitor of TNF- α synthesis trans-capsularly is advantageous over systemic treatment. Such advantages include, for example, arresting the inflammation process begun within the joint and the degeneration of the hyaline cartilage, preventing intracapsular nerve irritation, increasing the half life of the inhibitor of TNF- α synthesis in the capsule and reducing unwanted side effects (see the specification, for example at page 8, line 10 to page 10, line 5). Moreover, as discussed above, anti-TNF- α monoclonal antibodies, such as infliximab, are more specific for TNF- α whereas ENBREL[®] binds both TNF- α and lymphotoxin (TNF- β). Thus, there is no reasonable expectation of success in substituting an anti-TNF- α monoclonal antibody, such as infliximab,

with ENBREL[®] in the methods of Dunn. Thus, the claimed invention is not obvious. Hindsight reconstruction having Applicant's invention in mind is not permissible.

Braun teaches use of infliximab, a chimeric anti-TNF monoclonal antibody, to treat rheumatoid arthritis by intravenous (i.e., systemic) infusions. Braun does not teach or suggest that infliximab can be administered transcapsularly into the joint space. Therefore, Braun does not supply the teachings missing in Lehman and Dunn to arrive at the claimed invention.

The combined references do not teach or suggest a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Moreover, there is no motivation to modify the references in a manner which would do so. A *prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody or any biologic which inhibits TNF- α synthesis in Applicants' claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 91 and 92 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 91 and 92 under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics*, 140:125-127 (2002) and Dunn (EP 1 153 606) in view of Wolfrain *et al.* (U.S. Patent No. 6,756,215). The Office Action states that "[i]t would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating an inflamed orthopedic joint taught by Lehman and Dunn to administer a formulation additionally comprising a BMP or GDF as taught by Wolfrain *et al.*."

Applicants respectfully disagree. As noted above, Applicants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. The formulation can further comprise a growth factor. As amended, Claim 91 recites specific bone morphogenetic proteins and Claim 92 recites a specific growth differentiation factor. The Office Action states that "[i]t would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made

to modify the method of treating an inflamed orthopedic joint taught by Lehman and Dunn to administer a formulation additionally comprising a BMP or GDF as taught by Wolfrain et al.”

The standard for obviousness is discussed above. In addition, the teachings of Lehman and Dunn are discussed in detail above. ENBREL[®] is not known to inhibit TNF- α synthesis and ENBREL[®] is not an anti-TNF- α monoclonal antibody. While page 13 of the Office Action mailed June 27, 2006 states that “[t]he reference teaches the injection of a group of agents such as anti-cytokines (column 3, 2008, lines 45-57), which would by definition include an inhibitor of TNF- α synthesis” (emphasis omitted), nowhere does Dunn mention injecting an anti-TNF- α monoclonal antibody. Further, there were many anti-cytokines known in the art at the time of the invention. See, for example, Van Lent, PL. *et al.*, “Major Role for Interleukin 1 But Not For Tumor Necrosis Factor in Early Cartilage Damage in Immune Complex Arthritis in Mice,” *J. Rheumatol.*, 22: 2250-8 (Abstract) (Exhibit B), which discloses that anti-cytokines include, for example, anti-IL-1 antibodies. Of all the anti-cytokines known in the art at the time of the invention, it would not have been obvious based on the teachings of Dunn to select an anti-TNF- α monoclonal antibody.

Wolfrain teaches administration of functionalized TGF- β family protein fusions. It does not teach use of a BMP. The combined references do not teach or suggest trans-capsular treatment with an inhibitor of TNF- α synthesis, wherein the inhibitor of TNF- α synthesis is an anti-TNF- α monoclonal antibody. Wolfrain does not supply the teachings missing in Lehman and Dunn to arrive at the claimed invention.

Moreover, there is no motivation to modify the references in a manner which would do so. A *prima facie* case of obviousness has not been established because there is no teaching, suggestion, or motivation to use an anti-TNF- α monoclonal antibody which inhibits TNF- α synthesis in the claimed invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Christine M. Wise

Christine M. Wise

Registration No. 58,073

Telephone: (978) 341-0036

Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date:

January 6, 2010